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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,315	BLECK ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-18 and 20-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12-18, 20-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of an amendment filed 8/22/05 (The Amendment). In the Amendment the specification was amended, and thus the objection to the specification is withdrawn. Also in the Amendment, claims 1, 12, 13, 21, 29, 32-34, 39, 41, and 42 were amended and claims 11 and 19 were canceled. Presently claims 1-10, 12-18, and 20-42 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claim 21, 29, and 42 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Regarding claim 21, it is recognized that the Office Action mailed 5/18/05 in paragraph 11 stated that a certain recitation the claims would be remedial. Applicant has indeed amended to recite that which was recommended. The indefinite nature of claim 21 was two-fold: the lack of a definition in the specification of "signal sequence" renders this term unclear, because the specification only seems to define "secretion signal sequence", where claim 29 recites this limitation, thus casting doubt on the meaning of "signal sequence" and the recitation of "signal sequence was vague because a signal sequence is an amino acid sequence while the gene is a nucleic acid sequence. The remedial language suggested was only intended to correct the second

issue. There still is no clear definition of what is intended by "signal sequence". Again, this limitation will be read to encompass any sequence that specifically targets an encoded protein to a particular subcellular localization.

5. Claim 29 recites the limitation "said exogenous gene" in line 3. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 42 recites the limitation "said plurality of integrating vectors" in line 5. There is insufficient antecedent basis for this limitation in the claim.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. These claims are drawn to methods of making host cells with up to 100 of integrated copies of a retroviral vector. The examples given in the specification provide evidence for a maximum of approximately 13 integrated vectors. Further, the highest number of integrant seen in the art was 15 (Arai (Virology 260:109-115 (1999), newly cited, page 112, first paragraph; and Mathor (Proc Natl Acad Sci USA 93: 10371-10376 (1996), of record, Table 1). Although the specification refers to a serial transduction protocol, this is not exemplified, and no evidence is provided that increasing numbers of proviral integrations would not result in insertional toxicity. It would seem likely that perhaps up to about 50 integrations would be feasible, although it is highly unlikely that more than about 50 integrants could be achieved without inducing detrimental levels of cellular toxicity.

9. Claims 1-10, 12-18, and 20-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1, wherein step c) comprises repeating steps a) and b) a plurality of times to provide host cells comprising up to 50 integrated retroviral vectors, does not reasonably provide enablement for the method of claim 1 wherein steps a) and b) are repeated a plurality of times to provide host cells comprising greater than 50 to about 100 integrated retroviral vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a new rejection.

10. When making a proper enablement rejection one must consider a number of factors that have been delineated by In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. These claims are broadly drawn to methods of making host cells with up to 100 of integrated copies of a retroviral vector. Multiple examples provided in the prior art teach that increasing the number of retroviral integrants may lead to insertional mutagenesis or insertional toxicity. Arai teaches that high levels of proviral integration could result in "insertional mutations in essential genes" (page 112, first full paragraph, line 10). Coffin (Retroviruses, CSHL Press, 1997, newly cited) discusses potential safety concerns with regard to retroviruses in gene therapy. "Insertional mutagenesis by retroviral vectors is often cited as a safety concern....In situations where relatively few cells are modified, as in the case of gene transfer

into rare hematopoietic stem cells, the total number of insertion sites will also be small, and the risks are expected to be very low. The risks are higher in cases where large numbers of cells are transduced, which increases the number of independent integration events" (page 463, second full paragraph). As retroviral insertion appears to be an essentially random event, the nature of retroviral insertion events is highly unpredictable.

12. The examples provided by the inventors only provide evidence for about 13 integrations of the retroviral vector. Further, the highest number of integrant seen in the art was 15 (Arai (Virology 260:109-115 (1999), newly cited, page 112, first paragraph; and Mathor (Proc Natl Acad Sci USA 93: 10371-10376 (1996), of record, Table 1). Although the specification refers to a serial transduction protocol, this is not exemplified. Thus no evidence is provided that a greater number of integrations would not result in insertional toxicity and be detrimental to the survival of the cell, and neither the specification nor the art of record specifically teaches how to achieve greater than about 15 integrations. As stated above, however, it would seem plausible that about 50 integrant could be achieved. Therefore, in order to create cells with a greater than about 50 retroviral integrations, the skilled artisan would be forced to perform an undue level of trial and error-type experimentation. As such the specification is not enabling of the full scope of the claimed invention.

13. Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is

a **NEW MATTER** rejection. This is a new rejection necessitated by the amendment to the claims on 8/22/02.

14. Applicant has amended claim 41 to recite that "about 20 to about 100 integrated retroviral vectors" are present in the genome of the host cell. Applicant has failed to point to where in the specification support for this limitation can be found. Upon careful perusal of the originally filed specification, claims, drawings, and abstract, no support for this limitation could be found.

15. Page 4, lines 7-8 state that at least 2, 5 and 10 vectors will integrate. Page 5, line 4 states that at least 5 and at least 10 integrated copies would be present. Page 44, lines 25 and 26 states that "host cells contain from 2 to 100 copies of the integrated vectors, and preferably from 5 to 50 copies of the integrated vector". Then Examples 19, 22, 25, and 26 provide exemplification of numbers of integrants achieved. These are not expressed as number of integrants per cell, and as such no mention of 20 integrants is given. Further, as argued above, the maximal number of integrants apparent is about 13. Therefore, as the specification does not provide support for these new limitations, the limitations constitute impermissible new matter.

Claim Rejections - 35 USC § 102

16. Claim 42 stands rejected under 35 U.S.C. 102(b) as being anticipated by Primus (Cancer Res 53: 3355-361 (1993), of record).

17. The claim is drawn to a method for transducing host cells comprising providing a host cell and a plurality of retroviral vectors encoding a gene of interest, contacting the host cells with the retroviral vectors in order to transduce the host cells, repeating this a plurality of times to

produce host cells with multiple integrated retroviral vectors, clonally selecting a host cell expressing the gene of interest and purifying a protein encoded by the gene of interest.

18. Primus discloses (see the Abstract and Materials and Methods) a method of expressing the D612 monoclonal antibody in colon carcinoma cells, where the light chain, expressed from the vector pLNCXII, is first introduced in to the cells, followed by a vector encoding the heavy chain in a sequential manner. The transduced cells were clonally selected after drug selection. The fully functional IgG was purified form the cells.

19. Claim 42 stands rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,637,483 (Dranoff, of record). Dranoff discloses (see Examples 1-3 and 8) the production of B16 melanoma cells that express IL-2 and GM-CSF additionally with either IL-4 or γ-interferon, through serial retroviral infection of the cells with viruses encoding the different cytokines (Example 8). The last line of Example 3 states that the transduced cells were clonally selected. To perform the cytokine assays of Example 2 the cytokines were isolated.

20. Claim 41 stands rejected under 35 U.S.C. 102(b) as being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-1-376 (1996), of record). Claim 41 is drawn to a host cell comprising multiple integrated retroviral vectors created by the method of claim 1, where the host cell comprises about 20 to about 100 retroviral integrants. Although the method of claim 1 requires repeated transduction cycles, a host cell with multiple integrations produced in this way would be undistinguishable from cells comprising multiple integrated retroviral vectors produced any other way. Mathor discloses a clone of cells containing 15 retroviral integrations (see Table 1). A cell containing 15 integrants could certainly be construed to contain "about 20".

Response to Arguments

21. The Amendment in section 2, 3, 4, 5 asserts that the amendment to claim 42 introduces limitations not present in any of the references. On the contrary, claim 42 has not been amended to contain any element that is not disclosed in these references. The argument claims that the references must teach an MOI of 10-1000 and 10-100 integrant, however claim 42 does not contain these limitations.

22. The rejections of claim 1-5, 10, 18, 20, 21, and 41 under 35 U.S.C. 102(b) as being anticipated by Inaba; claims 1-5, 10, 18, 20, 21, 27-31, 40, and 41 under 35 U.S.C. 102(b) as being anticipated by Primus or Dranoff have been withdrawn due to the amendment to the claims on 8/22/05. None of these references teach of infecting with an MOI of 10-1000 and none teach 10-100 integrations of the retroviruses.

23. Claims 1-10, 12-14, 16-18, 21, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Arai (Virology 260:109-115 (1999), newly cited) as evidenced by Falqui (J Mol Med 77: 250-253 (1999), newly cited). This is a new rejection.

24. The claims are drawn to a method of transducing cells by contacting a host cell with a plurality of retroviral vectors encoding a gene of interest, wherein the host cells are transduced at an MOI of 10-1000, and the steps are repeated a plurality of times to give host cells comprising about 10 to about 100 integrated retrovirus vectors.

25. Arai discloses (Abstract, Material and Methods, Figures 1-3 and pages 110 and 112) a method of transducing host cells at a high MOI with a VSV-G pseudotyped retrovirus where the retrovirus is MoMLV-based. The retrovirus encodes β-galactosidase with a nuclear localization

signal, which based upon the broad reading of signal sequence presented above, constitutes a signal sequence. Arai discloses the transduction of 3Y1 cells at MOIs of 1, 3, 10, and 30 to give copy numbers of integrated viruses at 1.3, 2.8, 7.0, and 15, respectively (see page 112, middle of first paragraph and Figure 2). Thus Arai has clearly taught that greater than 10 integrants can be achieved a t a high MOI. Arai discloses the infections as a single step, failing to specifically disclose repeating the process to achieve the higher number of integrants. From the data in Arai, it is clear that an MOI of 30 gives 15 integrants while an MOI of 10 gives 7 integrants. As Arai has clearly established that at least 15 integrant can be achieved, this level of integrant would inherently also have been achieved by transducing with the relatively lower MOI of 10 multiple times in a serial fashion.

26. In fact Falqui clearly shows that serial transduction methods lead to increased levels of transduction, and increased levels of integration, leading to increased gene expression. The data presented by Falqui in both Figures 1 and 2 clearly shows that indeed a serial transduction protocol leads to higher level of integration. Figure 1 clearly shows that each of the single transduction protocols leads to only a small percentage of cells displaying a low level of green fluorescence. As shown in Figure 2, repeating the transduction just three times leads to not only an increased number of cells transduced, but also to an apparent increase in the number of retroviruses that integrate into each cell. That is, the single transfectants in Figure 1 barely fluoresce above 10 units, while the triple transduction protocol shown in Figure 2 shows a small number of cells that actually fluoresce above 100 units. As the same retrovirus with the same promoter is used in all cases the only plausible explanation for the increased fluorescence is more copies of the vector present, i.e. more integrants.

27. It is thus clear that Arai could easily have achieved high levels of integration by performing a serial transduction protocol. Arai would have necessarily performed the requisite number of repeated transductions until the desired level of integration and gene expression were achieved, thus each of claims 2-10 are anticipated. Further the retrovirus of Arai is produced from packaging cells that comprise gag-and pol genes and have been transfected with both the retroviral vector and a vector encoding the VSV-g envelope protein. By performing the protocol in a serial fashion, Arai would have necessarily performed the step described in claim 13. Further, using the disclosed method of a single transduction, Arai produced host cells with 15 integrant which can certainly be interpreted as "about 20".

Claim Rejections - 35 USC § 103

28. Claims 1-10, 12-14, 16-18, 20-22, 29, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falqui (J Mol Med 77: 250-253 (1999), newly cited) in view of Arai (Virology 260:109-115 (1999), newly cited). This is a new rejection.

29. Falqui discloses a MoMLV-based retroviral vector comprising two genes of interest, a truncated form of the nerve growth factor receptor (LNGFr) under the control of an SV40 promoter and human proinsulin (see Material and Methods 'Retroviral vector construction', page 250-251). As the proinsulin is measure by RIA in the culture media, this gene necessarily is operably linked to a segment encoding a signal sequence. Further the LNGFr is expressed on the surface so it too necessarily is fused to a signal sequence. Falqui further discloses a method of transducing the host cells by serially transducing. It is clearly apparent from the data presented in

Figures 1 and 2 that this serial transduction protocol leads to multiple integrations of the retrovirus in each cell (see above).

30. Falqui does not disclose the use of a vector pseudotyped with VSV-G. Further Falqui in no way discloses either the MOI used to transduce or the number of integrants that were achieved.

31. Arai discloses a VSV-G pseudotyped retroviral vector that is used in a method of transduction at an MOI of 1, 3, 10, and 30 resulting in 1.3, 2.8, 7.0, and 15 integrations per cell, respectively. Arai teaches that the retrovirus is produced in cells that have been transfected with the retroviral vector itself as well as the envelope VSV-G.

32. As Arai has shown that at least 15 retroviral integrations can take place. By utilizing the MOI of Arai, Falqui could clearly achieve at least 15 integrations by transducing a series of times at an MOI of 10. One would have been motivated to use the pseudotyping of the retrovirus as taught by Arai with the retroviral vector of Falqui because pseudotyped vectors have a broad host range and relatively high transduction efficiency with "another advantage over amphotrophic vectors in that pseudotyped vector particles are resistant to concentration by ultracentrifugation, making possible the convenient purification of virus stocks and the preparation of high-titer virus stocks (more than 1 x 109 infectious units (IU)/ml)" (page 109 second column, first full paragraph). It would have been obvious to one of ordinary skill in the art to utilize the pseudotyped viral particles of Arai with the retroviral construct of Falqui using the MOIs of Arai, in the serial transduction method of Falqui because both the high MOI of ARAI and the serial transduction protocol of Falqui can lead to increases in the level of both transduction efficiency and the number of retroviruses that will integrate in each cell. One would

have repeated the serial transduction protocol the number of times required to achieve the desired levels of retroviral integration and subsequent gene expression. One would have the reasonable expectation of success by combining the teachings of Falqui with those of Arai because Arai has clearly established, that although very high levels of retroviral integration, such as when infected with an MOI of 100 in the Arai paper, apparently leads to insertional cytotoxicity, Arai has also shown that at least 15 integrants is an acceptable level of retroviral integration.

33. Claims 1 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falqui and Arai as applied to claims 1, 12-14, and 16-18 above, and further in view of Clontech (CLONTECHniques, 4/1999 pages 8-9, of record). This is a new rejection.

34. As discussed above in paragraphs 29-32, Falqui and Arai combine to teach a method for transducing cells with a retroviral construct where repeated exposure of the cells to the retroviral construct is used to lead to increased numbers of integrated retroviral vectors and increased levels of protein expression, Falqui and Arai do not teach using 293-GP cells to produce pseudotyped retrovirus. Also even though the pseudotyping of Arai does indeed use cells that have been transfected with the retroviral construct and the envelope, the method of Arai uses a stable cell line transfected with the envelope, not cells that have been newly transfected, or cotransfected.

35. Clontech also teaches the technique of producing a retroviral vector that has been pseudotyped with VSV-G (whole article, see particularly figure 1). Indeed, the VSV-G retrovirus is produced by cotransfecting GP-293 cells, which have been engineered to express gag and pol from MoMLV, with the retroviral vector and a vector encoding VSV-G. One would have been

motivated to use a VSV-G pseudotyped retrovirus as taught by Clontech in the combined method and vector of Falqui and Arai because the method of pseudotyping as taught by Arai requires the additional step of activating Cre recombinase to induce expression of the VSV-G gene. The method of Clontech would be much more straightforward and amenable to a repeatable system because the transfection conditions could be adjusted while the packaging cells of Arai have a one-way activation of VSV-G which would ultimately lead to the killing of the packaging cells. The method as taught by Clontech does not have this problem. It would have been obvious to one of skill in the art to combine the teachings of Clontech with those of Falqui and Arai to because Falqui and Arai already use VSV-G together, while Clontech simply provides a further possible method for producing the pseudotyped retroviruses.

36. Claims 1, 12-14, 16, 17, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falqui and Arai as applied to claims 1, 12-14, 16, and 17 above, and further in view of Naldini (Science 272: 263-267 (1996), of record). This is a new rejection.

37. Falqui and Arai teach the limitations as described above in paragraphs 29-32. Falqui and Arai do not disclose the use of a lentiviral vector. Naldini discloses (see particularly Figure 1) a pseudotyped lentiviral vector that bears VSV-G as the retroviral receptor. One would have been motivated to use the lentiviral vector of Naldini in the transduction methods of Falqui and Arai because lentiviral vectors are particularly useful as they can "integrate into the genome of nonproliferating cells" (page 263, column 1, center of first paragraph). Therefore it would have been obvious to one of skill in the art to combine the teachings of Naldini with those of Mathor and Inaba to use a VSV-G pseudotyped lentiviral vector, because a VSV-G-expressing lentiviral

vector would allow for infection of nondividing cells and high level expression of the protein of interest.

38. Claims 1, 22-24, 27-34, 39, 40, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falqui and Arai as applied to claims 1, 22, and 29 above, and further in view of Primus (Cancer Res. 53:3355-3361 (1993), of record) and Deng (Biotechniques 25: 274-279 (1998), of record). This is a new rejection.

39. Falqui and Arai teach the limitations of the claims as described above in paragraphs 29-32. Falqui and Arai do not teach of the retrovirus comprising the heavy and light chains of immunoglobulin as the two genes of interest, where the two genes are expressed in a bicistronic fashion and the two genes comprise the heavy and light chains of immunoglobulin which may be IgG and those two genes are either expressed bicistronically from a single message, or as the gene of interest in two separate retroviruses. Falqui and Arai also do not teach of clonally selecting the cells and purification of the protein of interest.

40. Primus discloses (see the Abstract and Materials and Methods, page 3355, column 2, second full paragraph through page 3356, first full paragraph) a method of expressing the D612 monoclonal antibody in colon carcinoma cells, where the light chain, expressed from the vector pLNCXII, which contains MoMLV LTRs, is first introduced in to the cells, followed by the heavy chain in a sequential manner. The transduced cells were clonally selected after drug selection. As the product antibody was both secreted and expressed on the cell surface, the expressed chains necessarily were linked to secretion signals (see Figures 2-4). The fully functional IgG was purified form the cells. Thus Primus discloses the introduction of the two

genes of interest into the host cells, by using two separate retroviruses. Primus does not disclose expression of the two chains of the antibody in a single bicistronic vector.

41. Deng discloses (see particularly Figure 2) vectors for the bicistronic expression of two genes of interest using an internal ribosome entry site (IRES). The use of IRES-containing vectors was not yet widely practiced at the time of the Primus publication, but as the 1990s progressed this technique became much more common. Therefore, to simplify the process of producing cells that would express antibodies, the skilled artisan would have been motivated to combine the two separate vectors of Primus into a single IRES vector as taught by Deng. One would have been motivated to use the pseudotyped vector and serial transduction system of Falqui and Arai to express and purify antibodies using the retroviral vectors taught by Primus and Deng because the methods of Falqui and Arai allow for the high level expression of a protein of interest while avoiding excessive integration that may lead to integrational mutagenesis and efficient antibody production can provide a useful source of potentially therapeutically useful reagent. One would have had reasonable expectation of success because Falqui and Arai can clear efficiently infect cells for the expression of high levels of protein production while Primus has shown that functional antibodies can be produced in this manner, while Deng has shown that a bicistronic message is an efficient way to express two chains of protein. Therefore, it would have been obvious to on of skill in the art to combine the teachings of Falqui and Arai with those of Primus and Deng to achieve multiple integrations of the bicistronic retroviral vector and consequently high-level expression of the antibody.

42. Claims 1, 26, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falqui and Arai as applied to claim 1 above, and further in view of Schroder (Biotechnol Bioeng 53: 547-559 (1997), of record). This is a new rejection.

43. Falqui and Arai together disclose the methods of serial transduction with pseudotyped vector as described above in paragraphs 29-32. Falqui and Arai do not disclose the inclusion of an amplifiable marker, which can be DHFR, in the retroviral vector with the method also comprising growing the cells under conditions including for example methotrexate to get amplification of the integrated retroviral vectors. Falqui and Arai additionally do not disclose using CHO cells as the host cells for retroviral transduction.

44. Schroder discloses (see Abstract, Introduction, and Table I) the amplification of hATIII expression in CHO cells through DHFR-mediated amplification of the genes by treating with methotrexate. The skilled artisan would have been motivated to include an amplifiable marker such as DHFR, as taught by Schroder, in the retrovirus of Falqui and Arai for the increased production of the protein of interest because gene amplification is known to be an effective mode of increasing production of a protein of interest. The skilled artisan would have been motivated to use CHO cells, as taught by Schroder, in the protein production methods of Falqui and Arai because CHO cells are known to be an excellent model cell line for the high level production of a protein of interest. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teaching so Schroder with those of Falqui and Arai in order to achieve maximal protein production.

Response to Arguments

45. Each of the rejection under 35 U.S.C. 103(a) over Mathor in view of a variety of other references is withdrawn. Applicant's argument that the true MOI is not known based on Mathor's teachings is correct, although the reasoning for this differs from that presented by Applicant. Applicant asserts that there is no teaching in Mathor of at what stage the culture was transduced nor what volume was used to transduce. On the contrary a careful reading of the Material and Methods (page 10372, column 1, first full paragraph) shows that the cells were transduced by co-culturing, thus the only variable that would play a role is the size of the well and the volume of the media the cells were co-cultured in. As neither of these details is given, it is indeed impossible to truly know the MOI used by Mathor.

46. Applicant further argues that there is no motivation to combine as the prior art teaches that insertional mutagenesis is a potential problem. While it is agreed that the art indeed teaches that a *high* number of integrants would be detrimental, the art also clearly teaches that 15 integrants is not toxic to the cells (see page 112 of Arai). There is however motivation to produce a lower number of integrants, such as up to 50. The reasoning behind this is that it indeed seems reasonable that the instant application may be enabled up to about 50 integrants. There is however no distinction between what is taught in the specification and what is taught in the prior art. That is, while up to about 50 integrants may be possible, the Specification has only taught as many as about 13 integrants (see above). Clearly then the prior art has taught as many, and even more integrant as the applicants, i.e. 15 vs. 13, so the skilled artisan would be able to achieve the same levels professed by the applicants.

47. In short, the applicants provide no further evidence over that provided in the prior art that would distinguish the method of the invention with that already present in the prior art. Therefore, if the specification is indeed considered to be enabled for up to about 50 integrants, then there is no reason of record to suggest why the skilled artisan would not have been enabled and motivated to produce the same levels based strictly on the prior art. If indeed Applicant would suggest that the knowledge available in the art at the time of the invention would not be enabling in this way, then how could one suggest that the specification is enabling to this extent? In short one could not. Thus if the prior is not enabling, then there is no way the specification can be enabling.

48. Applicant repeatedly argues that there is no reasonable expectation of success and that the art is unpredictable. In making this argument, Applicant asserts that in a rejection in 10/397,079 the position was taken by the Office that the retroviral insertion is random and the nature of the insertions is unpredictable. It is noted that this line of argument was in reference to high level of integration in an enablement and written description rejection. The random nature of retroviral insertion was merely established to show that applicant's had not taught how to overcome the problems of insertional mutagenesis that are clearly established in the art in relation to high levels of retroviral insertion. As argue in paragraphs 46 and 47 above, this argument is only intended to apply to high levels of integration, i.e. greater than about 50 integrants. There has been no assertion that that achieving the relatively low level of 50 insertions would be expected to fail. Thus, the arguments presented in 10/397,073 regarding written description and enablement do not apply to the present situation. Therefore he skilled artisan would have had a reasonable expectation of success because both Mathor and Arai teach

that 15 integrants is possible, which is in excess of the 13 integrants that the specification teaches. Thus, the references are properly combined with a reasonable expectation of success.

Double Patenting

49. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

50. Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,852,510 (Bremel). This is a new rejection.

51. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claim 41, it is generic to all that is recited in the respective claim of the patent, i.e., the patented claims fall entirely within

the scope of instant claim 41. Instant claim 41 is drawn to any host cell comprising 20-100 integrated retroviral vectors. Patent claim 1 further limits the host cell such that it is clonally selected and there are 20-50 integrants. Further limitation is placed on the nature of the retroviral integrants. It is therefore clear that instant claim 41 is generic to patent claim 1.

52. Claim 41 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/397,079.This is a new rejection.

53. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, both the instant claim and the reference claim are claiming host cells with multiple integrated vectors. The only difference in the limitation of the host cell is in the number of integrants. It is noted however that the ranges of possible integrant overlap, and as MPEP 2144.05 states: "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists." Thus, the instant claim is not patentably distinct from the reference claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

54. Claim 41 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 103 of copending Application No. 11/018,895. This is a new rejection.

55. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, both the instant claim and the reference claim are claiming host cells with multiple integrated vectors. The instant claim is generic to all that is recited in the reference claim, except for the range of integrated vectors. It is noted however that the ranges of possible integrants overlap, and as MPEP 2144.05 states: "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists." Thus, the instant claim is not patentably distinct from the reference claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

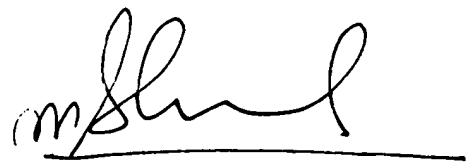
56. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633



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SUPERVISORY PATENT EXAMINER